**35 U.S.C. § 112, first paragraph**

All pending claims are rejected under the first paragraph of 35 U.S.C. § 112, allegedly for lack of an enabling disclosure. In particular, the Examiner has stated that the claims "read on a method of alleviating *any* (a) disease or disorder in *any* (an) affected animal cell by local delivery to the cell using *any* (a) reverse gene therapy vector encoding any (a) 'therapeutic gene product which is usually only expressed in cells of an abnormal tissue that is not afflicted with the disease or disorder'" and that "the specification fails to teach one skill in the art to envision what gene products are embraced by the claim language, particularly in the context consistent with the specification" (Office Action at 3).

"When rejecting a claim under the enablement requirement of section 112, the [E]xaminer bears the 'initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification.'" TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH-ENABLEMENT CHEMICAL/BIOTECHNICAL APPLICATIONS, section II, subsection B, page 5, *citing In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (see Appendix A). "To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the [E]xaminer must provide evidence or technical reasoning substantiating those doubts." *Id.* Applicants assert that the Examiner has not provided a tenable basis for rejecting the claims of the instant application.

The instant invention relates to a novel therapeutic approach to alleviating a disease or disorder. "Traditional gene therapy methods involve using a gene vector to deliver a wild type or engineered gene or a promoter operably linked with a nucleic acid encoding a wild type or engineered protein or a wild type or engineered RNA molecule to an [sic] cell of an animal afflicted with a disease or disorder" (Specification at 8, lines 8-11). Reverse gene therapy entails "localized delivery of a gene therapy vector which comprises a nucleic acid to an affected cell of an animal afflicted with a disease or disorder" and "the nucleic acid encodes a therapeutic gene product which is usually only expressed in cells of an abnormal tissue which is not afflicted with the same disease or disorder" (Specification at 8, lines 14-16). This approach is useful in instances where gene therapy works. The

unpredictability of gene therapy is therefore irrelevant.

The methods described in the instant invention utilize a "yin and yang" approach, where one cellular response associated with a disease/disorder is "countered" by administering a therapeutic gene product associated with an opposite cellular response. Additionally, the therapeutic gene product responsible for generating an opposing response is typically found in abnormal cells not afflicted with the disease or disorder to be treated.

> "The identity of the therapeutic gene product is not critical. This gene product need only be one which will alleviate the disease or disorder in the affected cells or tissues. When the disease or disorder is re-entry atrial flutter, the gene product can be any gene product that reduces myocardial conductivity in atrial tissue. Examples of such gene products include mutated ion channel proteins and their subunits."
>
> "Expression of such proteins/subunits is normally associated with a disease or disorder. However, when these proteins/subunits are expressed in atrial tissue in a subject afflicted with re-entry atrial flutter, conductivity of the tissue is reduced and the atrial flutter is alleviated."

Specification at 11, first full paragraph. It is apparent that the therapeutic approach is novel. The state of the art of gene therapy is not a tenable basis for rejection on non-enablement grounds since the methods of the present invention can be used to treat diseases and disorders where gene therapy has been successful.

The Examiner further references Eck *et al.* and Orkin *et al.* to describe the general status of gene therapy. Accordingly, the Examiner cites that "no successful gene therapy protocol was known" and "gene therapy has been oversold, and the impression that gene therapy is successful is mistaken" (Office Action at 4-5). The Examiner then additionally cites post-filing art regarding an unsuccessful gene therapy approach for cystic fibrosis by Boucher *et al.*

Whatever uncertainties may accompany any given prospective use of gene therapy, however, there can be no dispute that gene therapy is practicable and, indeed, has worked in several instances. For example, see Johannes, L., Gene Therapy Gets Boost From Hemophiliac Test, *Wall St. J.*, B1, June 7 (2001); Johannes, L., Second Chance: Gene Therapy, Much Maligned, Is Promising In Some Cancer Trials, *Wall St. J.*, A1 May 4 (2000); Henderson, C.W., Suicide Gene Therapy/Cytokine Vaccine Effective Against

Brain Tumors, *Gene Therapy Wkly.*, Oct. 5 (2000). Although it is the Examiner's position that "the general status of gene therapy art has not significantly changed" since the Orkin publication, Applicants have provided examples that indicate otherwise, including instances where gene therapy works.

Additionally, "[c]ompliance with the enablement requirement of 35 U.S.C. §112, first paragraph, does not turn on whether an example is disclosed" (M.P.E.P. § 2164.02), and "working examples are not required by the statute, rules, or the case law." TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH-ENABLEMENT CHEMICAL/BIOTECHNICAL APPLICATIONS, section III, subsection A(2), page 17 (see Appendix A). Thus, Applicants' working examples should not be the touchstone for the enabling quality of their specification.

Examiner asserts that "the specification fails to show [that] the expressed [HERG] protein influenced biophysical function of the $K^+$ channel in any way in myocytes *in vitro* or in a dog model *in vivo*, and it fails to show the delivered expression vector has any effect on reducing myocardial conductivity in atrial tissue and or in 'alleviating a disease or disorder'" (Office Action at 4). The Examiner also states that "the specification fails to demonstrate that merely delivering the vector encoding HERG (A561V) achieved any therapeutic effect" (Office Action at 11). The burden is not on the Applicants to show that HERG influenced biophysical function of a $K^+$ channel or that delivering HERG will achieve a therapeutic effect, rather, it is the Examiner's burden to show that delivering HERG will not achieve a therapeutic effect. It appears that the Examiner has relied on our working examples to ascertain that the specification is not enabling and the Examiner has not provided a reasonable basis for determining the present invention is not enabled. Lack of working examples is not a tenable position, as working examples are not required.

Additionally, the first paragraph of Section 112 does not require an applicant to demonstrate that each of the species within the genus in the claimed invention work, but how to make and use the claimed invention. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of Section 112 is satisfied." *Id.*, page 12, *citing In re Fisher*, 427 F.2d 833, 839 (1970) (see Appendix A). In keeping with above-quoted PTO guidelines, Applicants have described a method of

making and using a composition within their claims, and need not address in this regard every possible reverse gene therapy vector and therapeutic gene product which is usually only expressed in cells of an abnormal tissue that is not afflicted with the disease or disorder.

Lastly, the Examiner asserts that the disclosure to a defective HERG gene product is relied upon a reference to non-patent prior arts, improperly incorporated the subject matter into this application and that "it is not clear which reference disclosed the detailed structure and sequence of the vector which is used in the instant specification" (Office Action at 9).

Example 3, page 47 of the specification describes transfection of Chinese Hamster Ovary cells using vectors comprising mutant genes. Sanguinetti et al., Cell 81:299 describes the structure and sequence of the vector to be used in the instant invention.

**35 U.S.C. § 112, second paragraph**

The Examiner has also rejected claims 1-38 and 65-68 under 35 U.S.C. § 112, second paragraph, for indefiniteness. Specifically, the Examiner states that "a disease is 'a condition of the living animal or plant body or of one of its parts that impairs normal functioning'" and that "a cell could be a cultured cell such as those cultivated in tumor cell lines."

Applicants assert that a cultured cell is considered a part of a living animal or plant body that can be afflicted with a condition that impairs normal functioning. Ex vivo techniques are contemplated in the present invention (see, for example, specification at 17, lines 11-20) and the cells being treated are necessarily "cultured". "The reverse gene therapy compositions and methods described herein can be used to transform cells located outside the body of the animal" and "[f]ollowing transformation of cells outside the body tof the animal, the cells can be cultured, returned to the body of the same animal ..." (Specification at 21, lines 20-23). Furthermore, "[t]he cell can, for example, be a cultured cell, such as a cultured cell which is subsequently returned to the body of the animal from which the cell was obtained or is subsequently returned to the body of a second animal other than the animal from which the cell was obtained" (specification at 5, lines 7-20).

The Examiner further asserts that "the term 'reverse' in these claims and specification is used to mean 'undesirable'" and that "the accepted meaning in an English

dictionary is 'acting, operating, or arranged in a manner contrary to the usual'" (Office Action at 13).

The term "reverse," as used in the claims and specification, relates to "a nucleic acid construct which would be harmful if expressed in one physiological setting is delivered to a diseased physiological site in order to achieve the reverse (i.e. a beneficial) effect in a different setting" (specification page 8, lines 28-29 and page 9, lines 1-2). In other words, "reverse" indicates that the effect observed in the disease setting may be the "reverse" effect observed in a normal physiological setting. Contrary to the Examiner's assertions, therefore, "reverse" does not mean "undesirable" but instead simply connotes something contrary to what would be observed normally, i.e., something divergent from the usual.

Lastly, the Examiner rejects claim 1 because the specification does not define "abnormal," "usually" and "not afflicted" expressly, and because "there are no common structure or functions among claim recited gene products" (Office Action at 14). "Abnormal," "usually," and "not afflicted" have their common meanings in this context, however, and a person skilled in the art surely would understand what sort of therapeutic gene products are involved. Thus, "abnormal" is defined as "different from what is usual or average, esp. in a way that is not desirable," "usual" is defined as "happening, done or used most often," and "afflict" means "to make someone suffer physically or mentally." CAMBRIDGE INTERNATIONAL DICTIONARY OF ENGLISH, Cambridge University Press, 2000.

Again, Applicants would emphasize that the claimed invention establishes a technology platform with relevance to the various instances where gene therapy is feasible. Against this backdrop, the skilled person would find interpreting these terms a straightforward exercise, informed as they are by common usage. Applicants therefore respectfully request that the Examiner withdraw this rejection.

## CONCLUSION

Applicants submit that this application is in condition for allowance, and they solicit an early indication to that effect. Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, a telephone call to the undersigned, at the telephone number listed below, is courteously invited.

Respectfully submitted,

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